IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No.: 5256
WILLIAMS *et al.*	Art Unit: 1652
Appl. No.: 09/839,946	
(Appeal No. 2007-1159)	Examiner: Saidha, T.
Filed: April 19, 2001	Atty. Docket: 2057.0090003/BJD/SAC
For: **PEG-Urate Oxidase Conjugates and Use Thereof**	

Second Declaration of Merry R. Sherman Under 37 C.F.R. § 1.132

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Sir:

I, the undersigned, **Merry R. Sherman**, declare and state that:

1. I am a co-inventor of the above-captioned U.S. patent application number 09/839,946, filed April 19, 2001, entitled, "PEG-Urate Oxidase Conjugates and Use Thereof."

2. I am also the Chief Executive Officer and President of Mountain View Pharmaceuticals, Inc. ("MVP"), a co-assignee of the present application by virtue of an assignment from David L. Williams, Mark G. P. Saifer and Merry R. Sherman to MVP executed on September 29, 1999, and recorded in the U.S. Patent and Trademark Office on November 30, 2001, beginning at Reel No. 012320, Frame No. 0564.

3. My *curriculum vitae* is attached as **Exhibit A**.

4. I have reviewed the above-identified patent application and the file history thereof including the Decision on Appeal dated July 18, 2007. I would like to

MRS

discuss the commercial preparation of porcine liver urate oxidase (catalog number U3250) from Sigma that was disclosed in Lee *et al.*, Science 239:1288-1290 (1988). I would also like to clarify several statements made in my first Declaration of Merry R. Sherman Under 37 C.F.R. § 1.132 dated May 25, 2005 (hereinafter "my first Declaration").

5. As discussed in our Brief on Appeal filed April 20, 2006, uricase preparations such as those available from Sigma (including Sigma Cat. No. U3250, the particular commercially available uricase used in the studies in Lee) contain substantial quantities (*i.e.*, more than 10%) of non-tetrameric forms of the enzyme. This contention is supported by the present specification which discloses that the same commercial preparation of uricase used in Lee (Sigma U3250) had to be purified by the methods disclosed in the present specification in order to obtain a uricase preparation in which greater than 90% of the uricase was in the tetrameric form. *See* specification at page 20, lines 9-13. For completeness, I note that the present specification describes the commercial preparation of Sigma porcine liver uricase as "Porcine liver uricase...obtained from Sigma-Aldrich, St. Louis, MO, catalog No. *U2350*...." (emphasis added). However, this transposition of numbers is a typographical error in the specification and the catalog number in the specification should read "U3250." As evidence of this typographical error, copies of a purchase order from Mountain View Pharmaceuticals, Inc. to Sigma-Aldrich (dated May 5, 1998), a packing list from Sigma Aldrich (dated May 5, 1998), an invoice from Sigma Aldrich to Mountain View Pharmaceuticals, Inc. (dated May 5, 1998), and a label from a vial of U3250 (dated "rec'd 5-7-98") are attached as **Exhibits B, C, D and E**, respectively. These exhibits

show that Sigma catalog number U3250 is porcine liver uricase and that Mountain View Pharmaceuticals, Inc., a co-assignee of the present application, ordered and received a vial of Sigma catalog number U3250 in May of 1998. A vial of Sigma catalog number U3250 was used in experiments disclosed in Example 1 of the present application.

6. The contention that uricase preparations prior to the present invention contained substantial quantities of the non-tetrameric form of the enzyme is further supported by the actual size-exclusion chromatograms of several preparations of uricases, including the Sigma commercial preparation used in Lee. These preparations of uricase, which are described below, were analyzed on a Superdex®-200 size-exclusion chromatography column by the Applicants of the present invention prior to purifying the uricases using the methods described in the present application. These chromatograms were obtained prior to the filing of U.S. Provisional Application No. 60/219,318 from which the present application claims priority. *See* attached Figures 3-5.

7. Figure 3 shows a size-exclusion chromatogram of the commercial preparation of Sigma porcine (also known as hog) liver uricase (Catalog No. U3250) that was used in the methods of Lee and was also used in Example 1 of the present application. Figure 3 demonstrates that prior to purifying the uricase using the methods described in the present application, Sigma porcine liver uricase (Catalog No. U3250) contained only 62% tetramer along with 21% octamer and 17% aggregates larger than octamer.

8. Figure 4 shows a size-exclusion chromatogram of a commercial preparation of Sigma porcine (also known as hog) liver uricase (Catalog No. U3377) that

was also used in Example 1 of the present application. Figure 4 demonstrates that prior to purifying the uricase using the methods described in the present application, Sigma porcine liver uricase (Catalog No. U3377) contained only 86% tetramer along with 11% octamer and 3% aggregates larger than octamer.

9. Figure 5 shows size-exclusion chromatograms of a recombinant preparation of soybean uricase that was used in Example 6 of the present application. The chromatograms show the soybean uricase preparation before and after the uricase preparation was purified using the methods described in the present application. In addition, Figure 5 shows a size-exclusion chromatogram of a commercial preparation of *Candida utilis* uricase (Sigma Catalog No. U1878) that was used in Example 4 of the present application.

10. Figure 5 demonstrates that prior to purifying the recombinant soybean uricase, the uricase contained only 65% tetramer along with 22% octamer and 13% aggregates larger than octamer. However, after the recombinant soybean uricase was purified using the methods described in the present application, 98% of the uricase was in the tetrameric form.

11. Figure 5 also demonstrates that prior to purifying the uricase using the methods described in the present application, *Candida utilis* uricase (Sigma Catalog No. U1878) contained only 55% tetramer along with 21% octamer, 19% aggregates larger than octamer, and 4% smaller than tetramer.

12. These data clearly show that the Sigma porcine liver uricase (U3250) that was used in Lee does not contain greater than 90% tetrameric uricase. In addition, these

data clearly demonstrate that other commercial, natural and recombinant uricase preparations contained significantly less than 90% tetrameric uricase prior to purifying the uricase preparations using the methods described in the present application. Accordingly, without specifically purifying the uricase preparations according to the methods described in the present application, the uricase preparations disclosed in Lee would not have contained greater than 90% tetrameric uricase.

13. With regard to my first Declaration, I wish to clarify several statements made in paragraph 8 of that Declaration. In that Declaration, I discussed Figures 1 and 2, which were disclosed in U.S. Patent No. 6,783,965 ("the '965 patent") as Figures 2 and 3. Mountain View Pharmaceuticals, Inc., is an assignee of the '965 patent.

14. Figure 1 illustrates size exclusion HPLC analysis on a Pharmacia Superdex® 200 column (1x30 cm) of the load and selected fractions from a preparative Mono Q chromatography of porcine uricase containing the mutations R291K and T301S (PKS uricase) showing data obtained by a light-scattering detector at a 90° angle (upper curves) and by absorbance at 276 nm (lower curves). Figure 2 illustrates size-exclusion analyses of fractions from a Mono Q column, showing data obtained by a light-scattering detector at 90° and by absorbance at 276 nm, as in Figure 1.

15. To further clarify paragraph 8 of my first Declaration, the top and bottom panels of Figures 1 and 2 represent the *same* samples of PKS uricase; however, as indicated above, the top panel shows the samples of PKS uricase detected by light scattering and the bottom panel shows the samples of PKS uricase detected by absorbance at 276 nm.

16. Figures 1 and 2 illustrate that octamers and larger non-tetrameric aggregates account for greater than 10% of the uricase present in isolated natural and recombinant uricase preparations, such as those disclosed in Lee. However, by using the methods described in the present specification, we were able to isolate fractions of uricase wherein greater than 90% of the uricase was in the tetrameric form. *See, e.g.*, fraction 6 in Figure 1 and fraction 7 in Figure 2. Thus, these data clearly demonstrate that the purification procedures disclosed in the present application are required in order to obtain the presently claimed isolated mammalian uricases in which greater than 90% of the uricase is in the tetrameric form. Accordingly, as indicated above, without having been purified according to the methods of the present application, the uricase preparations disclosed in Lee would not have contained greater than 90% tetrameric uricase.

17. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the present patent application or any patent issued thereon.

Respectfully submitted,

Merry R. Sherman

Merry R. Sherman, Ph.D.

Date: Sept. 14, 2007

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MERRY RUBIN SHERMAN, PH.D.
Chief Executive Officer and President
Mountain View Pharmaceuticals, Inc.

Education:

Wellesley College, Wellesley, MA	B.A.	1961	Chemistry
University of California, Berkeley, CA	M.A.	1963	Biochemistry
University of California, Berkeley, CA	Ph.D.	1966	Biophysics
Weizmann Institute, Rehovot, Israel	Postdoctoral	1966-1967	Polymer Science
National Institutes of Health, Bethesda, MD	Fellowships	1967-1970	Biochemistry

Research Positions:

1970-1976 Research Associate and Associate, Department of Surgical Research, Sloan-Kettering Institute (SKI), New York, NY

1975-1976 Visiting Investigator, Cardiovascular Research Institute, University of California Medical Center, San Francisco, CA

1975-1986 Head, Endocrine Biochemistry Laboratory, SKI

1/92-8/92 Visiting Scientist, New York University Medical Center, New York, NY

1993-1995 Pharmaceutical Consultant, Mountain View, CA

1995-present President, Mountain View Pharmaceuticals, Inc.

2005-present Chief Executive Officer, Mountain View Pharmaceuticals, Inc.

Academic Positions: *Positions at Cornell University Graduate School of Medical Sciences (CUGSMS), New York, NY, were concurrent with those at SKI*

1971-1972 Instructor in Biochemistry, CUGSMS, New York, NY

1972-1977 Assistant Professor of Biochemistry, CUGSMS

1977-1986 Associate Professor of Biochemistry, CUGSMS

1986-1993 Professor of Biochemistry, Rutgers University, Newark, NJ

Honors:

1957 Finalist, National Science Talent Search

1960 Elected to *Phi Beta Kappa*

1985 Outstanding Woman Scientist Award, Association for Women in Science, Metropolitan New York Chapter

1987 Distinguished Alumna Award, New Rochelle High School, New Rochelle, NY

Editorial Boards and Refereeing:

1974-1978 Editorial Board, *Endocrine Research Communications*

7/78-6/81 Editorial Board, *Journal of Biological Chemistry*

7/82-6/84 Editorial Board, *Journal of Biological Chemistry*
Occasional reviews for:
Anal Biochem, Arch Biochem Biophys, Biochemistry, Cancer Research, Endocrinology, Nature, Proc Natl Acad Sci USA, Steroids

Special NIH Study Sections: 2/77, 1/79, 12/82, 5/85 and 4/91

National Committees:

9/84-6/88 Program Committee of The Endocrine Society

12/85-6/88 Board of Scientific Counselors, Natl. Institute of Child Health and Human Dev.

Professional Memberships: American Society of Biological Chemists, The Endocrine Society, American Association for Cancer Research, Society for Neuroscience, Association for Women in Science, American Association of Pharmaceutical Scientists.

Selected Publications:

Rubin MM, Katchalsky A (1966). Mathematics of band centrifugation: Concentration-independent sedimentation and diffusion in shallow density gradients. Biopolymers 4:579-593.

Rubin MM, Changeux J-P (1966). On the nature of allosteric transitions: Implications of non-exclusive ligand binding. J Mol Biol 21:265-274.

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O'Malley BW, **Sherman** MR, Toft DO (1970). Progesterone "receptors" in the cytoplasm and nucleus of chick oviduct target tissue. Proc Natl Acad Sci USA 67:501-508.

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O'Malley BW, Toft DO, **Sherman** MR (1971). Progesterone-binding components of chick oviduct. II. Nuclear components. J Biol Chem 246:1117-1122.

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Sherman MR, Stevens Y-W, Tuazon FB (1984). Multiple forms and fragments of cytosolic glucocorticoid receptors from human leukemic cells and normal lymphocytes. Cancer Research 44:3783-3796.

Sherman MR, Stevens J (1984). Structure of mammalian steroid receptors: Evolving concepts and methodological developments. Annu Rev Physiol 46:83-105.

Gorsline J, Bradlow HL, **Sherman** M R (1985). Triamcinolone acetonide 21-oic acid methyl ester: A potent local antiinflammatory steroid without detectable systemic effects. Endocrinology 116:263-273.

Maayani S, **Sherman** M R (1990). Adenylate cyclase-linked 5-hydroxytryptamine receptors in the brain. *in:* Serotonin: From Cell Biology to Pharmacology and Therapeutics, (Paoletti R, Vanhoutte PM, Brunello N, Maggi FM, *eds.*). Dordrecht, The Netherlands, Kluwer Academic Publishers, pp. 39-51.

Smith R A, Balis F M, Ott K H, Elsberry D D, **Sherman** M R, Saifer M G P (1995). Pharmacokinetics and tolerability of ventricularly administered superoxide dismutase in monkeys and preliminary clinical observations in familial ALS. J Neurol Sci 129 (Suppl):13-18.

Saifer MG P, Williams L D, **Sherman** M R, French J A, Kwak L W, Oppenheim J J (1997). Improved conjugation of cytokines using high molecular weight poly(ethylene glycol): PEG-GM-CSF as a prototype. Polymer Preprints 38:576-577.

Sherman MR, Williams L D, Saifer MG P, French J A, Kwak L W, Oppenheim J J (1997). Conjugation of high molecular weight poly(ethylene glycol) to cytokines: Granulocyte-macrophage colony-stimulating factors as model substrates. *in:* Poly(ethylene glycol) Chemistry and Biological Applications. ACS Symposium Series 680, (Harris J M, Zalipsky S, *eds.*). Washington, DC, American Chemical Society, pp. 155-169.

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Sherman MR, Saifer, MGP, Perez-Ruiz, F (2007). PEG-uricase in the management of treatment-resistant gout and hyperuricemia. Adv Drug Deliv Rev doi:10.1016/j/addr.2007.06.011.

Patents and Published Patent Applications

Williams LD, Hershfield MS, Kelly SJ, Saifer MGP, **Sherman** MR (2003). PEG-urate oxidase conjugates and use thereof. US Patent No. 6,576,235 B1, Mountain View Pharmaceuticals, Inc., and Duke University, Jun. 10, 2003.

Williams LD, Hershfield MS, Kelly SJ, Saifer MGP, **Sherman** MR (2005). PEG-urate oxidase conjugates and use thereof. European Patent No. EP 1 100 542 B1, Mountain View Pharmaceuticals, Inc., and Duke University, Jun. 22, 2005.

Sherman MR, Saifer MGP, Williams LD, Hershfield MS, Kelly SJ (2004). Aggregate-free urate oxidase for preparation of non-immunogenic polymer conjugates. US Patent No. 6,783,965 B1, Mountain View Pharmaceuticals, Inc., and Duke University Aug. 31, 2004.

Sherman MR, Saifer MGP, Williams LD, Hershfield MS, Kelly SJ (2001). Aggregate-free urate oxidase for preparation of non-immunogenic polymer conjugates. PCT Patent Publication No. WO 01/59078 A2, Mountain View Pharmaceuticals, Inc., and Duke University, Aug. 16, 2001.

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Saifer MGP, Martinez AL, Williams LD, **Sherman** MR (2004). Polymer conjugates of interferon-beta with enhanced biological potency. PCT Patent Publication No. WO 2004/060299 A2, Mountain View Pharmaceuticals, Inc., published Jul. 22, 2004.

Bhaskaran SS, **Sherman** MR, Saifer MGP, Williams LD (2004). Polymer conjugates of cytokines, chemokines, growth factors, polypeptide hormones and antagonists thereof with preserved receptor-binding activity. US Patent Application No. 2004/0136952 A1, Mountain View Pharmaceuticals, Inc., published Jul. 15, 2004.

Bhaskaran SS, **Sherman** MR, Saifer MGP, Williams LD (2004). Polymer conjugates of cytokines, chemokines, growth factors, polypeptide hormones and antagonists thereof with preserved receptor-binding activity. PCT Patent Publication No. WO 2004/060300 A2, Mountain View Pharmaceuticals, Inc., published Jul. 22, 2004.

Purchase Order

Mountain View Pharmaceuticals, Inc.
3475-S Edison Way
Menlo Park, CA 94025-1813

DATE	P.O. NUMBER
5/5/98	623

VENDOR	SHIP TO
Sigma-Aldrich P.O. Box 18817B St. Louis, MO 63160 800-325-3010	Mountain View Pharmaceuticals, Inc. 3475 Edison Way Suite S Menlo Park, CA 94025-1813

ORDER NUM.	TERMS	SHIP VIA	FOB	ACCOUNT
134479	Net 30			49509304

ITEM	DESCRIPTION	UNITS	QTY	UNIT PRICE	AMOUNT
U-3250	Uricase, porcine liver, Type I, suspension in 2.0 M (NH4)2SO4	~~10~~ 20 units	~~1~~ 2	~~115.25~~ 198.45	~~230.50~~ 198.45
T 3253	Trizma Hydrochloride, 250 g	250 g	1	38.15	38.15
U 5128	Urea, 1 kg	1 kg	1	23.05	23.05
			Total		$291.70

SIGMA-ALDRICH

SIGMA ▪ 3500 DEKALB STREET ▪ ST. LOUIS, MO 63118 USA
Customer Service 800-325-0070 and Technical Service
800-325-5832
Fax 800-325-5052
http://www.sigma.sial.com

SHIP TO:

MOUNTAIN VIEW PHARMACEUTICALS
KEN OLSEN
3475 EDISON WAY / STE S
MENLO PARK CA 94025

DATE	SOLD TO ACCT.	SOLD TO NAME	PURCHASE ORDER NUMBER	REFERENCE #	DELIVERY #
05/05/1998	49509304	MOUNTAIN VIEW PHARMACEUTICALS	623	134479	80150919

ROUTE	PERSON TO CONTACT	PHONE NUMBER	PAGE
AIRBORNE 2 DAY FCA SHIPPING POINT	JOHN FRENCH	6503653315	1 of 1

STOCK NO.	LOT NO.	ORDERED	SHIPPED	BACK ORD.	DESCRIPTION
U3250-25UN	070H8000	1	1	0	URICASE TYPE I PURIFIED FROM PORCINE LIVER
U5128-1KG	067H0571	1	1	0	UREA ACS REAGENT
T3253-250G	087H5412	1	1	0	TRIZMA HYDROCHLORIDE REAGENT GRADE

Rec'd 5/7/98

SOLD TO:
MOUNTAIN VIEW PHARMACEUTICALS
3475 EDISON WAY / STE S
MENLO PARK CA 94025

ORIGINAL

INVOICE

Please include invoice # on remittance.

INVOICE NUMBER
90170114
SHIP DATE/INVOICE DATE
05/05/1998 05/05/1998
TERMS/DUE DATE
N30 06/04/1998
SOLD TO CUSTOMER NUMBER
49509304
PURCHASE ORDER NUMBER
623

BILL TO:
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3475 EDISON WAY / STE S
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SIGMA-ALDRICH

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FEIN: 43-1742718

FOR GENERAL INFORMATION

Sigma - 800-521-8956 Supelco - 800-247-6628
Aldrich, Fluka, Riedel-de Haën - 800-771-6737
e-mail: sigald@sial.com Home Page: http://www.sigald.sial.com
Phone Collect from Anywhere in the World (314)771-5750

MATERIAL NUMBER / HTS CODE / BATCH NUMBER	DESCRIPTION / COUNTRY OF ORIGIN / SHIP TO CUSTOMER NUMBER / SHIP TO CITY / CONTACT	SHIPPED FROM / SHIPPED TO	DELIVERY NUMBER / BOX NUMBER / ROUTING	QUANTITY	UOM	UNIT PRICE	EXTENDED PRICE
U3250-25UN 070H8000	URICASE TYPE I PURIFIED FROM PORCINE & US / 49509304 / MENLO PARK JOHN FRENCH 6503655515	SIGMA CHE CA 94025	80150919 AIRBORNE	1.000	EA	198.45	198.45
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			SUB TOTAL				259.65
			TRANS / HANDLING				9.93
			TOTAL TAX				21.40
			TOTAL AMOUNT DUE				290.98

BA010405
5/27/98

Exhibit D
Appl. No. 09/839,946
SKGF Ref No.: 2057.009000/3/BJD/SAC

FCA

Total Amount Due 290.98

Currency USD

Page 1 / 1

Jon Richard
Manager

BATMAN 05/08/1998

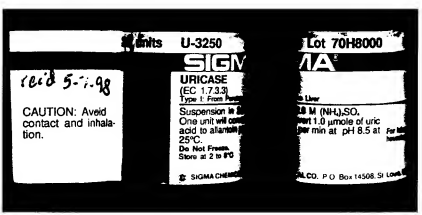


Figure 1
Appl. No. 09/839,946
SKGF Ref No.: 2057.0090003/BJD/SAC

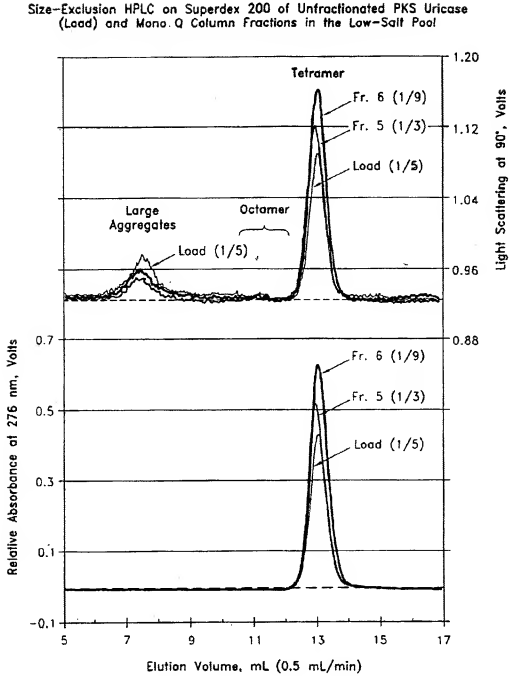
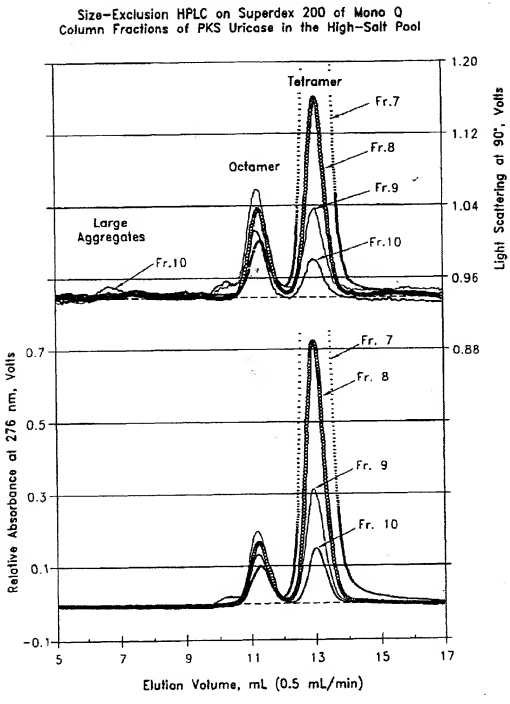


Figure 2
Appl. No. 09/839,946
SKGF Ref No.: 2057.0090003/BJD/SAC



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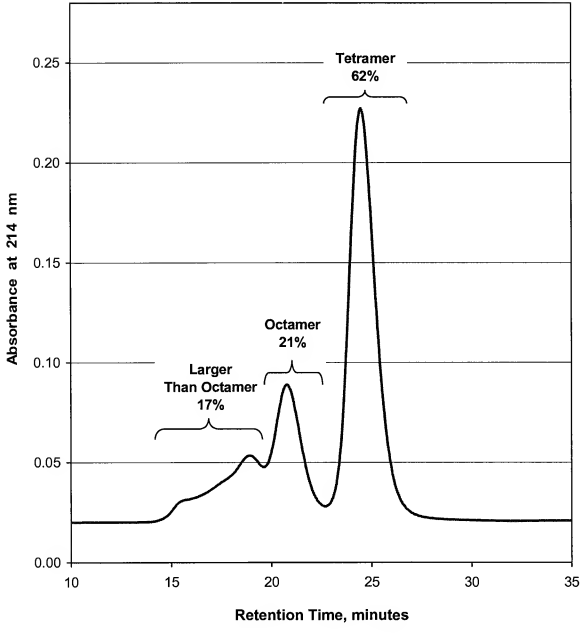
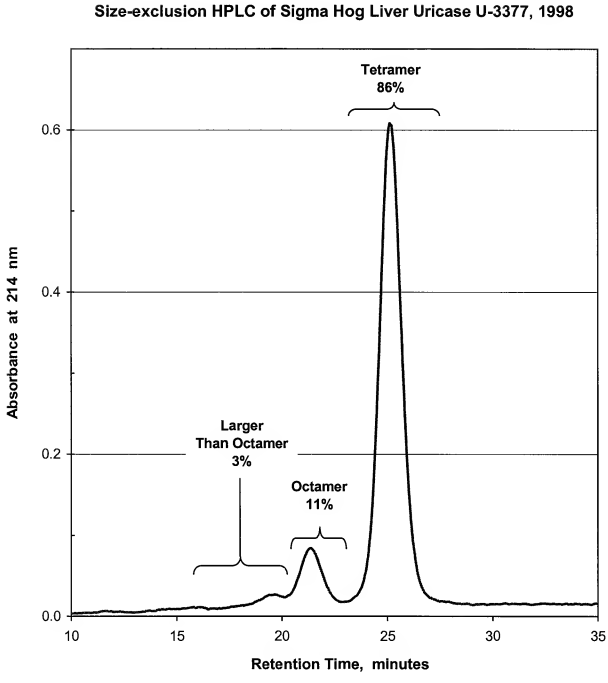
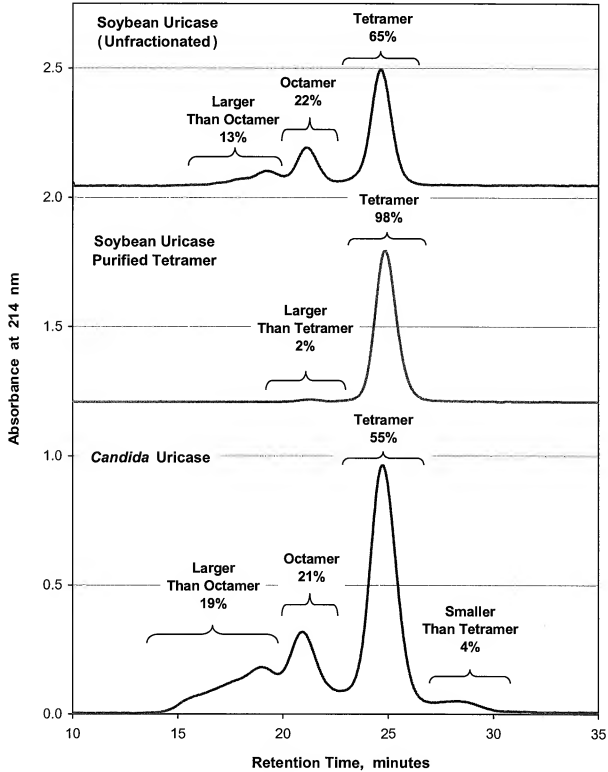


Figure 4
Appl. No. 09/839,946
SKGF Ref No.: 2057.0090003/BJD/SAC



Size-exclusion HPLC of Recombinant Soybean Uricase and Its Tetramer (Purified by Williams *et al.*) and of *Candida* Uricase, 1998



980312a02, 980210c03

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